MECHANISM OF ŒDEMA IN CHRONIC SEVERE ANÆMIA

BY

L. M. SANGHVI, V. S. SHARMA, AND G. MANSHARAMANI

From the Department of Cardiology, Sawai Man Singh Hospital and Medical College, Jaipur, India

Received June 5, 1962

Cardiovascular adjustments that develop in chronic anæmia have been studied by many investigators. Studies of renal circulation in anæmia, however, are few (Bradley and Bradley, 1947; Whitaker, 1956). A characteristic reversible renal functional abnormality has been described in chronic anæmia. It has been suggested that œdema, which occurs in a large number of cases of anæmia on some basis other than decreased plasma osmotic pressure or increased venous pressure, may be secondary to renal retention of salt and water, possibly attributable to glomerulotubular imbalance (Bradley and Bradley, 1947) or abnormal tubular reabsorption (Whitaker, 1956). Abnormalities of renal function in chronic anæmia in patients with œdema have, however, not been reported. The present investigation of circulatory abnormalities, particularly of renal circulation, was undertaken to determine the ætiological factor of œdema in patients with chronic severe anæmia.

Subjects and Methods

Forty-five patients, 36 men and 9 women, admitted to the hospital for treatment of chronic anæmia of not less than three months' duration and with hæmatocrit values of less than 30 per cent were selected for this study. Their ages ranged between 14 to 50 years with an average of 30 years. Œdema was present in 25 patients, 17 men and 8 women, in 8 of whom congestive heart failure was considered to be present. Dyspnœa, œdema of feet, and hepatic enlargement, which are usual manifestations of congestive heart failure, also occur in uncomplicated chronic anæmia. Heart failure was, therefore, considered to be present after careful consideration of these factors, and of elevated venous pressure, clinical and radiological evidence of pulmonary congestion, and rapid regression in size of the enlarged tender liver with improvement of the anæmia. The duration of symptoms of anæmia varied between four months and three years with an average of 15 months. The duration of anæmia was presumably much longer, and was due to hookworm infestation in 21 cases, chronic dysentery in 13, bleeding hæmorrhoids in 4, and chronic malaria in 2 cases, and was of undetermined ætiology in 5 cases. The hæmatocrit values ranged between 8 and 28 per cent with an average of 14·4 per cent: they were up to 10 per cent in 18, between 11 and 19 per cent in 16, and 20 and 28 per cent in 11 cases. Care was taken to exclude patients with hypertension or any renal or cardiovascular disorder apart from anæmia, which might interfere with the circulatory abnormalities. The laboratory data were obtained on admission in each patient, but could be obtained after treatment in only 14 patients as it was found difficult to persuade patients for follow-up study after they were cured. The data were also obtained in 20 others to serve as normal controls.

Hæmatocrit values were determined by Wintrobe's (1956) method. Serum proteins were determined by the copper sulphate specific gravity method of Moore and Van Slyke (1930). Hypoproteinæmia was considered to be present if total serum proteins were less than 6 g. and albumin less than 3·5 g. per 100 ml. Venous pressure was determined by direct method. Cardiac output (CO) was estimated in a fasting basal state by the dye dilution method using Evans Blue (Kinsman, Moore, and Hamilton, 1929; Newman *et al.*, 1951). Total blood volume (TBV) and plasma volume (PV) were determined by the method of Gibson and Evans (1937) simultaneously with the determination of the cardiac output, and values were calculated per kg. body weight. Total vascular resistance (TVR) was calculated from the cardiac output and the mean arterial blood pressure (diastolic pressure plus one-third of pulse pressure).

Renal hæmodynamics were studied in a fasting basal state following ingestion of 1500–2000 ml. water. Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were estimated by inulin and diodrast clearances respectively, as described by Goldring and Chasis (1944). Renal blood flow (RBF) was calculated from the ERPF and the hæmatocrit. No correction of ERPF and RBF has been made in this study for the extraction ratio of diodrast. Filtration fraction (FF) was calculated as GFR per 100 ml. ERPF. Renal vascular resistance (RVR) was calculated from RBF and the mean arterial blood pressure. Renal fraction of the cardiac output (RF/CO) was used to express renal blood flow as a percentage of total cardiac output. Values of GFR, ERPF, and RBF have been presented in the results as corrected to 1·73 m.^{2} body surface area.

Results

The mean values and ranges of the laboratory data in normal controls and in anæmic patients are given in Table I. The incidence of significant alterations of data is given in Table II. For the

TABLE I

Mean Values and Ranges of Laboratory Data in Normal Controls and Patients*

	Control	All cases	Cases without œdema	Cases with œdema		
				All cases	Without failure	With failure
No. of cases	20	45	20	25	17	8
Hematocrit (percentage)	42 (36–45)	14·4	17·5 (9–28)	12	13 (9–23)	10 (7–16)
CO (l./min.)	5 (3·5–6·1)	7·7	7·5 (4·6–10·9)	7·9	7·7 (4·6–14·1)	8·2 (5·6–11·3)
TBV (ml./kg.)	82 (63–104)	84	82 (47–119)	87	87 (57–106)	87 (50–111)
PV (ml./kg.)	45 (32–58)	72	66 (38–98)	77	76 (46–91)	78 (66–98)
TVR (dynes/sec./cm.$^{-5}$)	1250 (1100–1900)	848	852 (445–1320)	845	860 (370–1341)	813 (470–980)
RVR (dynes/sec./cm.$^{-5}$)	7300 (5900–8900)	17550	11892 (7180–25020)	22092	19230 (9290–31860)	28170 (15220–47580)
GFR (ml./min.)	125 (95–160)	80	95 (47–151)	69	70 (36–108)	67 (29–106)
ERPF (ml./min.)	730 (460–960)	396	493 (270–640)	320	360 (160–575)	235 (146–358)
RBF (ml./min.)	1190 (780–1550)	470	600 (299–780)	366	415 (180–640)	262 (162–387)
FF (percentage)	19 (11–29)	21·4	19·7 (8·7–36)	22·8	20·7 (7·9–31)	27·1 (17·4–45)
RF/CO (percentage)	22 (16–25)	5·5	7·4 (4–13·1)	3·9	4·4 (2·2–8·7)	3·0 (1·4–4·32)

* Figures in parenthesis are ranges.

Abbreviations: CO=Cardiac output; TBV=Total blood volume; PV=Plasma volume; TVR=Total vascular resistance; RVR=Renal vascular resistance; GFR=Glomerular filtration rate; ERPF=Effective renal plasma flow; RBF=Renal blood flow; FF=Filtration fraction; RF/CO=Renal fraction of cardiac output.

purpose of this study the data have been divided in two main groups, 20 cases without œdema and 25 with œdema, and the latter further subdivided into 17 cases without congestive failure and 8 with failure.

The cardiac output was increased in 31 patients, 18 of whom had œdema, and was more than 8 l./min. in 17 patients, 10 of whom had œdema. It was normal in 14 patients, 7 of whom had œdema and the heart rate was less than 80 in 9 of them. The stroke volume was increased in 22 and the heart rate was more than 90 in 5 of the 31 with increased cardiac output. The total blood volume was normal in 34 patients, 17 of whom had œdema; increased in 7, 5 of whom had œdema;

TABLE II

INCIDENCE OF SIGNIFICANT ALTERATIONS OF LABORATORY DATA

Group of cases	Total cases	No. of cases with								
		GFR <95	ERPF <460	ERPF <360	RBF <500	RF/CO <6%	RVR >15000	CO >6·1	CO >8	Serum albumin <3·5g.%
No œdema	20	7	10	2	5	6	4	13	7	8
Oedema:										
No failure	17	16	14	9	12	15	11	11	6	8
Failure	8	6	8	8	8	8	8	7	4	5
Total cases	45	29	32	19	25	29	23	31	17	21

and decreased in 4 patients, 3 of whom had œdema. The plasma volume was increased in 37 patients, 22 of whom had œdema. The total vascular resistance was decreased in 38 patients, 24 of whom had œdema. Serum proteins were decreased and hypoproteinæmia was present in 21, of whom 13 had œdema. The renal vascular resistance was more than 10,000 dynes/sec./cm.$^{-5}$ in 13 patients without and 23 with œdema: it was more than 15,000 in 4 patients without and 19 with œdema, including all 8 with congestive failure. The glomerular filtration rate was decreased in 7 patients without, and 22 with œdema, and was normal in others. The effective renal plasma flow was decreased in 10 patients without, and 22 with œdema. The renal blood flow and renal fraction of cardiac output were decreased in every patient. The RF/CO was less than 6 per cent in 6 patients without, and 23 with œdema. The filtration fraction was increased in 6 patients, 5 of whom had œdema including 4 with congestive failure.

The relation between hæmatocrit range and mean values of data is given in Table III. The

TABLE III

MEAN VALUES OF DATA ACCORDING TO HÆMATOCRIT RANGE

	Hæmatocrit percentage		
	8–10	11–19	20–28
Total cases	18	16	11
CO	8·2	7	7·4
TBV	85	80	88
PV	77	71	65
TVR	778	902	900
RVR	22360	16409	11360
GFR	69	88	88
ERPF	337	390	490
RBF	377	460	630
RF/CO	3·7	5·9	8
FF	21·8	22·9	18·3

ERPF, RBF, and RF/CO progressively decreased, and RVR increased with decrease of hæmatocrit: the GFR decreased considerably when the hæmatocrit was 10 per cent or less, and FF showed no significant change.

The laboratory data were repeated after improvement of anæmia in 14 patients, 5 without œdema and 9 with œdema; including 2 with heart failure (Table IV). ERPF increased in all cases except one without œdema, RBF and RF/CO increased and RVR decreased in every case; GFR increased in 11; and FF decreased in 7 patients. Of 5 patients without œdema, GFR increased in

TABLE IV

RENAL FUNCTION DATA BEFORE AND AFTER TREATMENT IN 14 PATIENTS*

Case No.	Age and sex	RVR	GFR	ERPF	RBF	RF/CO	FF	Hæmatocrit percentage
1	30 M	17470	51	432	569	4·8	11·7	24
		7690	75	719	1198	21·3	10·5	40
2	30 M	15140	104	475	563	6·2	21·8	15
		6340	108	818	1363	22·3	13	40
3	16 M	11050	62	552	747	11	11·2	26
		6200	93	826	1530	20	11·2	46
4	23 M	14480	100	460	523	5	21·8	12
		5550	105	855	1652	21·2	12·3	44
5	25 F	13280	84	532	626	5·7	15·8	15
		10290	86	537	767	13	16·3	30
6	30 F	12880	84	450	585	4	18·6	23
		7650	106	562	997	18·2	18·6	40
7	50 M	11340	41	518	582	8·7	8	12
		7600	85	700	1110	23·2	12·2	40
8	50 M	22730	50	323	355	3·6	15·5	9
		10430	110	576	795	13	19	32
9	15 M	16310	79	421	467	4·4	18·8	9
		10390	86	644	1056	24·3	13·4	39
10	25 M	31140	36	209	230	4·3	17·5	9
		9048	98	587	937	14·7	16·8	37
11	20 M	29990	72	294	335	4·5	24·6	12
		9095	92	750	1102	22·5	12·3	32
12	32 F	31860	58	210	230	2·5	27·8	9
		9160	89	762	1070	14·3	11·7	29
13	30 F	36480	44	251	276	4·3	17·4	9
		6920	80	821	1392	—	9·8	41
14	24 F	28290	56	205	220	2·4	27·5	7
		6290	145	974	1411	26·3	15	31
				Mean	values			
Cases 1–5, no œdema	Before	14284	80	490	605	6·5	16·4	18
	After	7214	93	751	1302	19·5	12·6	40
Cases 6–12 with œdema	Before	23320	60	346	398	4·6	18·7	12
	After	9050	95	654	1009	18·6	14·8	36
Cases 13,14 with failure	Before	32385	50	228	248	3·4	20·9	8
	After	6605	112	897	1401	—	12·4	36
14 cases	Before	20888	66	380	450	5·1	18·2	14
	After	8045	95	724	1168	19·5	13·7	37

* Upper figures are before treatment and lower ones after treatment. Cases 1–5 are without œdema, 6–12 with œdema, and 13–14 with failure.

2 with no significant change in 3, and FF decreased in 2 patients. Of 7 patients with œdema and 2 with heart failure, GFR increased in all of them. FF showed no change in 2, increased in 2, and decreased in 3 of the former 7 patients and both those with failure. Plasma volume decreased in all the 14, while total blood volume decreased significantly in 8 patients, 3 without œdema and 5 with œdema, including 2 with failure. Cardiac output decreased in 10 out of 12 in whom it was repeated and slightly increased in 2 patients. Alterations in the mean values during the anæmic

state expressed as a percentage of values after treatment in these 14 patients compare well with alterations in anæmic patients expressed as a percentage of normal control values (Table V).

TABLE V

MEAN VALUES ON ADMISSION EXPRESSED AS PERCENTAGE OF CONTROL MEAN VALUES IN ALL CASES OF ANÆMIA, AND AS PERCENTAGE OF MEAN VALUES AFTER TREATMENT IN 14 CASES WITH REPEAT STUDY

	All anæmia cases (Percentage of control values)				Cases with repeat study (Percentage of values after treatment)			
	Without œdema	With œdema		Total	Without œdema	With œdema		Total
		Without failure	With failure			Without failure	With failure	
No. of patients	20	17	8	45	5	7	2	14
Hæmatocrit	41	31	24	34	45	33	22	36
CO	150	154	164	154	155	149	—	151
TBV	100	106	106	102	116	113	122	115
PV	160	170	170	160	160	152	166	157
RVR	163	263	400	240	196	246	490	250
GFR	76	56	54	64	86	63	45	69
ERPF	68	50	32	54	65	53	25	52
RBF	50	35	22	40	48	39	18	38
RF/CO	34	20	14	25	33	24	—	27
FF	104	105	142	112	130	125	170	132

DISCUSSION

Strauss and Fox (1940) suggested that anæmia *per se* was a factor conducive to water retention. Bradley and Bradley (1947) reported striking abnormalities of renal circulation in chronic anæmia, particularly renal vasoconstriction and a large reduction of renal blood flow despite increased cardiac output. They observed that the mean values of GFR, ERPF, and RBF, respectively, were decreased by 32, 25, and 46 per cent in male patients and that the filtration fraction was within the lower portion of the normal range with little change in it after treatment. They thought that renal vasoconstriction in chronic anæmia occurred in both the afferent and the efferent arterioles but predominantly in the efferent ones since the filtration fractions were low. In view of the consistent changes in renal function these investigators suggested that œdema occurring in patients with anæmia may be secondary to renal retention of salt and water, possibly attributable to glomerulo-tubular imbalance indicated by the reduction of the filtrate rate/glucose Tm ratio, and normal Tmg. in most of the cases. Whitaker (1956) observed an increase of GFR, ERPF, and RBF, and a decrease of RVR in most of his cases after treatment of anæmia and no gross abnormality of the filtration fraction with no consistent change after treatment. There was no consistent relation between the fall in renal vascular resistance with treatment and the change in the filtration fraction, which suggested that renal vasoconstriction did not affect the afferent or the efferent arterioles predominantly. In addition there was no significant increase in GFR after recovery in 3 of his 4 cases with congestive failure suggesting that abnormal tubular reabsorption was responsible for impairment of salt and water excretion.

In the present study it was noted that the hæmatocrit was less than 20 per cent in all cases with œdema except two, although there was no parallel relation between hæmatocrit and œdema. Normal cardiac output was usually associated with slower heart rates (Sanghvi, Sharma, and Misra, 1957), and increased stroke volume rather than high heart rate was the important factor in maintaining a high output (Stewart, Crane, and Deitrick, 1937; Bishop, Donald, and Wade, 1955; Whitaker, 1956). The heart rate, the stroke volume, or the total vascular resistance showed no relation to the occurrence of œdema. It has been reported that the total blood volume may be decreased in anæmia (Gibson, Harris, and Swigert, 1939; Sharpey-Schafer, 1944; Wintrobe 1946),

and Bäckman (1961) recently noted that it was less decreased in iron deficiency anæmia than in megaloblastic anæmia. The total blood volume was within the normal range and the plasma volume was increased in a majority of our patients, both those with and those without œdema, thus showing that in iron deficiency anæmia in this study the decrease of red cell mass is compensated by an increase in plasma volume so that the total blood volume remains at about the normal level. The mean values of cardiac output and plasma volume were slightly more increased in patients with œdema and this was attributable to a lower hæmatocrit, but the levels of total blood volume showed no significant differences. No significant differences were thus observed between the abnormalities of general circulation in patients without œdema and patients with œdema except those that could be attributed to slightly lower hæmatocrit values in the latter. Hypoproteinæmia was found in 13 patients with œdema, which may have partly contributed to the occurrence of œdema. There was, however, no œdema in 8 patients with hypoproteinæmia, and hypoproteinæmia was not present in 12 patients with œdema. The data therefore showed that œdema in patients with anæmia could not be attributed either to the changes in the general circulation or to hypoproteinæma but was due to some other factor.

Study of renal circulation confirmed that completely reversible abnormalities of renal function occur in chronic anæmia. The most consistent changes were reduction of renal blood flow and renal fraction of the cardiac output, which were found in every case in this series. The present study also revealed significant differences between abnormalities of renal function in patients with œdema and in those without œdema (Table V). In 20 patients without œdema the mean values of GFR, ERPF, RBF, and RF/CO, respectively, were decreased by 24, 32, 50, and 66 per cent. The mean value of RVR, however, was increased by 63 per cent. Reduction of renal blood flow occurred despite increase of mean value of cardiac output by 50 per cent. RVR was more than 15,000 in 4 patients and ERPF and GFR were decreased in 10 and 7, respectively (Table II). The ERPF and GFR were within the lower portion of the normal range in most of the others and the filtration fraction was within the upper portion of the normal range in the majority.

In 17 patients with œdema and without congestive failure the mean values of GFR, ERPF, RBF, and RF/CO, respectively, were decreased by 44, 50, 65, and 80 per cent. The mean value of cardiac output was increased by 54 per cent and of RVR by 163 per cent. RVR was more than 15,000 in 11, and ERPF was decreased in 14 and GFR in 16 patients. In 8 with failure the mean values of GFR, ERPF, RBF, and RF/CO, respectively, were decreased by 46, 68, 78, and 86 per cent, the GFR was decreased in 6 patients and the ERPF was decreased and the RVR was more than 15,000 in all of them, and mean value of RVR was increased by 300 per cent and that of FF by 42 per cent.

The present study demonstrates that while abnormalities of renal function occur in uncomplicated chronic anæmia, they are greater in patients with œdema and are greatest in those with congestive heart failure. The results, therefore, strongly favour the assumption that œdema in chronic anæmia is due to renal retention of salt and water. In patients with œdema, the GFR, ERPF, RBF, and RF/CO were decreased more and the RVR increased more while the FF showed no consistent change. In patients with failure the ERPF, RBF, and RF/CO were still more decreased and the RVR greatly increased, and the FF also was increased. It was noted that the GFR was decreased significantly in cases with œdema but was not further decreased in patients with failure. Again the filtration fraction was within the normal range in most of the patients both without œdema and with œdema in the absence of failure but was increased or high normal in patients with failure. Observations made after improvement of anæmia showed decrease of renal vascular resistance and increase of renal blood flow in all patients, increase of glomerular filtration rate in 78 per cent of them particularly in all those with œdema, and no consistent change in filtration fraction with tendency to fall in some cases particularly those with congestive failure. The results of the present study thus show that in chronic anæmia there is renal vasoconstriction affecting the afferent arterioles with consequent reduction of renal blood flow. Absence of any consistent change in filtration fraction shows that the vasoconstriction also occurs in efferent arterioles so that

the filtration equilibrium across the glomerular membrane is apparently maintained at a normal level. The tendency for the filtration fraction to decrease after improvement of the anæmia in some cases, particularly in those with congestive heart failure, shows that efferent vasoconstriction may even be predominant in some cases.

Œdema in chronic severe anæmia may be attributed to "glomerulo-tubular imbalance". In man a quantity of fluid equal to the entire plasma is filtered and reworked every 25 minutes (Smith, 1956) and some 1200 g. salt a day are filtered, but sodium balance is maintained, and thus huge quantities of water and salt must be reabsorbed. These reabsorbed quantities must somehow be so delicately adjusted with the filtered amounts that the "balance" must be appropriate and subject to precise regulation. This intrarenal balance is termed "glomerulo-tubular balance". Barker (1960) states that many workers have tried hard to determine which of the two factors, i.e. alteration of the glomerular factor and filtered load or of tubular factor and tubular reabsorption, is responsible for changes in salt and water excretion. He states that from the available data this question is not easily decided and that all that can be said at present is that the change is in the "balance" between the glomerular and tubular factors, and when œdema occurs "glomerulo-tubular imbalance" must exist. In the present study GFR was decreased in most of the cases with œdema, but there was no constant relation between the two, as the GFR was also decreased in some cases without œdema. Again while the RBF and RF/CO were decreased and the RVR increased much more in cases with œdema than in those without œdema, no constant correlation could be observed between œdema and these factors. It is possible that decreased glomerular filtration rate may have significantly altered the tubular reabsorption or may itself have caused decreased excretion of sodium and water. It is also possible that marked reduction of renal blood flow may have altered tubular reabsorption of sodium and water. It is, therefore, likely that "glomerulo-tubular imbalance" exists in cases of chronic anæmia with œdema and that decreased renal blood flow, which is related to both filtration and tubular transfers, contributes to renal retention of salt and water by causing this imbalance.

SUMMARY

Circulatory abnormalities have been studied in 45 patients with chronic severe anæmia, of whom 25 had œdema, including 8 with congestive heart failure.

In most of the patients there was increased cardiac output and plasma volume, normal total blood volume, and decreased total vascular resistance. Œdema could not be attributed to these abnormalities of general circulation or to hypoproteinæmia.

A study of renal circulation showed decreased effective renal plasma flow, renal blood flow, and renal fraction of cardiac output, increased renal vascular resistance, and decreased or low normal glomerular filtration rate. These abnormalities increased with severity of the anæmia but there was no consistent relation between the hæmatocrit and renal function.

The hæmatocrit was less than 20 per cent in most of the patients with œdema. Renal circulatory abnormalities were greater in patients with than in those without œdema. The glomerular filtration rate was significantly decreased in patients with œdema, and the filtration fraction increased in those with failure. It is concluded that renal vasoconstriction occurs in both the afferent and the efferent vessels in patients without œdema, that greater vasoconstriction occurs in patients with œdema without heart failure, and that the greatest vasoconstriction, predominantly in efferent vessels, occurs in patients with heart failure. It is also concluded that œdema in chronic anæmia is due to renal retention of salt and water probably as a result of glomerulo-tubular imbalance.

Dr. L. R. Sarin, Superintendent, Sawai Man Singh Hospital, kindly permitted the publication of this report.

REFERENCES

Bäckman, H. (1961). *Scand. J. clin. Lab. Invest.*, **13**, suppl. 57.

Barker, E. S. (1960). In *Edema. Mechanisms and Management*, ed. J. H. Moyer and M. Fuchs, p. 504. Saunders, Philadelphia and London.

Bishop, J. M., Donald, K. W., and Wade, O. L. (1955). *Clin. Sci.*, **14**, 329.
Bradley, S. E., and Bradley, G. P. (1947). *Blood*, **2**, 192.
Gibson, J. G., 2nd., and Evans, W. A., Jr. (1937). *J. clin. Invest.*, **16**, 301.
——, Harris, A. W., and Swigert, V. W. (1939). *J. clin. Invest.*, **18**, 621.
Goldring, W., and Chasis, H. (1944). *Hypertension and Hypertensive Disease*, p. 195. Commonwealth Fund, New York.
Kinsman, J. M., Moore, J. W., and Hamilton, W. F. (1929). *Amer. J. Physiol.*, **89**, 322.
Moore, N. S., and Van Slyke, D. D. (1930). *J. clin. Invest.*, **8**, 337.
Newman, E. V., Merrell, M., Genecin, A., Monge, C., Milnor, W. R., and McKeever, W. P. (1951). *Circulation*, **4**, 735.
Sanghvi, L. M., Sharma, R., and Misra, S. N. (1957). *Circulation*, **15**, 373.
Sharpey-Schafer, E. P. (1944). *Clin. Sci.*, **5**, 125.
Smith, H. W. (1956). *Principles of Renal Physiology*. Oxford University Press, New York.
Stewart, H. J., Crane, N. F., and Deitrick, J. E. (1937). *J. clin. Invest.*, **16**, 431.
Strauss, M. B., and Fox, H. J. (1940). *Amer. J. med. Sci.*, **200**, 454.
Whitaker, W. (1956). *Quart. J. Med.*, **25**, 175.
Wintrobe, M. M. (1946). *Blood*, **1**, 121.
—— (1956). *Clinical Hematology*, 4th ed., p. 367. Lea and Febiger, Philadelphia.